

Dear Editors and Reviewers:

Thank you for your useful comments and suggestions concerning our manuscript entitled "*Efficacy and safety of laparoscopic Uncut Roux-en-Y anastomosis for radical distal gastrectomy: a systematic review and meta-analysis*" (Manuscript NO: 73438), which contributed to improve our manuscript, as well as important in guiding our research. Your comments have been carefully considered and the revision has been made according to them, marked in red in this edited version of our manuscript. The main corrections in the manuscript and the answers to the reviewers' comments are listed below:

Reviewer 1:

Comments 1: TITLE Comment: In this study, efficacy and safety of URY was evaluated by comparison between URY and BB. Therefore, the title may be better to include "comparison between URY and BB". Please consider revising the title. e.g. Comparison of efficacy and safety between laparoscopic uncut Roux-en-Y and Billroth II with Braun anastomosis after distal gastrectomy for gastric cancer: A meta-analysis.

Response: Thank you for your useful suggestion. The title has been revised as follow, according to your suggestion: "Comparison of efficacy and safety between laparoscopic uncut Roux-en-Y and Billroth II with Braun anastomosis after distal gastrectomy for gastric cancer: A meta-analysis".

Comments 2: INTRODUCTION Page 5, first sentence of the third paragraph: "Gastrointestinal reconstruction is an important part of GC surgery, tumor resection and lymph node dissection, ..." **Comment:** I think "as well as" should be added before tumor resection and lymph node dissection. "Gastrointestinal reconstruction is an important part of GC surgery as well as tumor resection and lymph node dissection, ..."

Page 5, third sentence of the third paragraph: "However, the incidence of short-term complications is high in the BI group due to excessive anastomotic tension, such as gastrointestinal fistulas classified as Clavien-Dindo grade IIIa or higher[11-13]."

Comment: Please consider revising this sentence as follows: "However, the incidence of short-term complications, such as gastrointestinal fistulas classified as Clavien-Dindo grade IIIa or higher, is high in the BI group due to excessive anastomotic tension

[11-13].” Page 6, lines 5-7: However, the Roux-Y stasis syndrome (RSS) has an incidence of 10-30% due to the abnormal activity in the distal jejunum of the anastomosed stomach[15]. However, the postoperative biliary reflux without RSS can be reduced by performing BII combined Braun (BB) anastomosis[16, 17]. Comment: “However” is used repeatedly. The latter “However” should be revised to “On the other hand” etc.

Response: Thank you for your useful suggestion. The relevant sections have been revised according to your suggestions to make the article easy to understand.

#Comments 3: MATERIALS AND METHODS Literature search strategy Page 6: ... using PubMed, Embase, Web of science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, CBM, and VIP. Comment: Please define abbreviations “CBM” and “VIP”. Statistical analysis Page 8: Publication bias was not performed because less than 10 studies were included. Comment: The meaning of “Publication bias was not performed” is unclear. Did the authors mean “Evaluation of publication bias was not conducted”?

Response: Thank you for your useful comment. The abbreviations "CBM" and "VIP" have been defined in the materials and methods. This sentence has been revised as follows: “Evaluation of publication bias was not conducted because less than 10 studies were included”.

#Comments 4: META-ANALYSIS Postoperative complications Page 13: Bile reflux Comment: I wonder the difference between the definitions of bile reflux and residual gastritis because bile reflux causes residual gastritis. In fact, in reference 31 (Wang, 2021), “bile reflux gastritis” at 3 months and 6 months was evaluated. Did bile reflux in this study mean bile reflux gastritis at 3 months and 6 months? Please clarify that.

Response: Thank you for your useful comment. Bile reflux means the reflux of bile into the stomach. Bile can easily enter the stomach after gastrectomy, causing a series of discomforts such as acid regurgitation, which can lead to reflux gastritis over time. Inflammation and bleeding may occur in the gastric mucosa, as observed using gastroscopy. The seven included articles have been carefully read; five of them reported

reflux gastritis and two reported bile reflux. Therefore, bile reflux has been changed to reflux gastritis and the meta-analysis has been re-conducted.

#Comments 5: DISCUSSION Page 15, lines 6-7: at a site 5 cm proximal to the gastrojejunostomy using different methods[37]. Comment: The meaning of “different methods” is unclear. Please describe specifically. Page 16, lines 5-7: In addition, our results on postoperative length of stay and URY that did not increase the postoperative length of stay were the same as those obtained by Park, et al[38] and Chen, et al[39]. Comment: There may be a grammatical error in this sentence. Did the authors mean “In addition, URY did not increase the postoperative length of stay compared to BB, which was consistent with results of Park, et al[38] and Chen, et al[39]”.? Page 16, lines 16-18: This result is probably due to the fact that duodenal secretions are diverted though the jejunojejunostomy to the distal jejunum after URY anastomosis compared to BB anastomosis[16] and the preservation of the original normal electrical conduction and direction of conduction in the limb that was uncut during the URY procedure[37]. Comment: There may be a grammatical error in this sentence. Please ask English editing service and revise this sentence appropriately.

Response: Thank you for your useful suggestion. Different methods of jejunal occlusion without transection have been defined in the article.

We have modified the sentence as “In addition, URY did not increase the postoperative length of stay compared to BB, which was consistent with results of Park et al.[38] and Chen et al.[39]”. Moreover, this sentence has been revised as follows: “This result is probably due to the fact that duodenal secretions are diverted to the distal jejunum though the jejunojejunostomy after URY anastomosis compared to BB anastomosis[16]. The uncut limb during the URY procedure preserved the original normal electrical conduction and direction of conduction[37]” to make it easier to understand.

#Comments 6: REFERENCES 23 Wells GA SB, O’Connell D, Peterson J, Welch V, Losos M. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. <http://www.ohrca/programs/clinicalepidemiology/oxfordhtm>

Accessed 2009 Oct 19. 2014: DOI: Comment: Reference number 23 has incorrect author name, link, and access date. Please modify as follows: Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2021 Dec 11.

Response: Thank you for your useful suggestion. Reference 23 has been revised according to your comment.

#Comments 7: Figure 1 Comment: The position of the first right-pointing arrow is shifted downward. Please correct it to the proper position.

Response: Thank you for your useful comment. The position of the first right arrow in Figure 1 has been modified.

#Comments 8: Table 1 Comment: Although Gender section is described as 14/14 in the Chen 2018 study, this description is incorrect because the number of BB cases is 30. Please correct.

Response: Thank you for your kind suggestion. The original literature has been reviewed and modified.

Reviewer 2:

#Comments 1: All the literature from this meta-analysis came from China. This suggests that this may be an emerging topic, but may not be one that has that much clinical significance as well as external validity internationally. The authors did recognize that this may be due to the increased incidence of gastric cancer in the East. Was wondering if efforts to retrieve any grey literature in this topic was attempted, such as from regions with similar high incidence of gastric cancer (eg. Korea, Japan, Mongolia). This might help to strengthen the conclusions drawn from this meta-analysis.

Response: Thank you for your useful suggestion. A systematic search has been performed in eight databases, with no restrictions on language or population. The following databases were also used in our search, such as clinicaltrials.gov (clinicaltrials.gov), Data Archiving

and Networked Services (DANS), the WHO International Clinical Trials Registry Platform (ICTRP), and Search Portal (apps.who.int/trialsearch/), the reference lists of articles and relevant conference proceedings. A study from Korea with three cases in the BII anastomosis group did not use Braun anastomosis (DOI: 10.5230/jgc.2014.14.4.229); thus, it was excluded. In addition, literature from regions with high incidence of gastric cancer (e.g., Korea, Japan, Mongolia) was not found.

#Comments 2: The heterogenous nature of this meta-analysis, by including both cohort studies as well as randomized controlled trials, makes it hard for the reader to summarise the conclusions. In this case, it might be more important to only include the randomized controlled trials (of which I note there are 3).

Response: Thank you for your useful suggestion. In this study, a subgroup analysis was performed based on whether the included studies were randomized controlled trials. Our analysis revealed that heterogeneity did not change significantly with the change in study type.

#Comments 3: I suspect a skewed funnel plot with publication bias will be detected, given that this topic is likely to have grey literature, particularly amongst groups who did not find any differences in bile reflux. A statement to mention the efforts made to search through grey literature to minimise publication bias, as well as attempts to include studies from not just China, will be useful.

Response: Thank you for your useful suggestion. A supplementary search has been conducted, resulting in no additional articles that matched the inclusion criteria.

#Comments 4: Meta-analyses of surgical trial always run the risk of pooling results with significant inter-operator differences as a result of differences in surgeon technique, surgeon experience, hospital caseload, and resources for postoperative care. The techniques of the 2 anastomosis methods employed by each individual study should be scrutinised (particularly amongst the 3 randomized controlled trials), and a statement should be made that these techniques were sufficiently similar such that the results can

be pooled.

Response: Thank you for your useful suggestion. the two anastomosis methods in the included studies have been carefully read, and enough similarities among the individual studies were found. In addition, the two methods are described in detail in the discussion.

#Comments 5: The authors used the term "anastomotic fistula". I think internationally, the more commonly employed term is "anastomotic leakage".

Response: Thank you for your useful suggestion. "Anastomotic fistula" has been changed to "anastomotic leakage" in the revised version.

#Comments 6: References 26, 28, 30 all reported postoperative ileus and gastroparesis. I feel the authors should clarify the differences in terminology between these 2 for the general audience.

Response: Thank you for your useful suggestion. The definition of postoperative ileus and gastroparesis has been clarified in the section of the definitions.

#Comments 7: Providing a pictorial representation of the uncut Roux-en-Y gastrojejunostomy anastomosis as well as the modified Bilroth II Braun anastomosis, might help bring across the discussion point pictorially.

Response: Thank you for your useful suggestion. the images of the uncut Roux-en-Y gastrojejunostomy and the modified Bilroth II Braun anastomosis have been added in the revised version.

#Comments 8: Much as the study findings concluded differences in bile reflux and residual gastritis between the 2 techniques, the consequences of such findings was not adequately elaborated. Will be important for the audience who is researching on the differences between these 2 techniques, and impact future clinical practice.

Response: Thank you for your useful suggestion. After a carefully reading of the included studies, bile reflux has been changed to reflux gastritis, and the impact on the results was described in the discussion.

#Comments 9: The scarcity of publication on these 2 topics except in China, does raise questions on the clinical implications and external validity of this study globally. Perhaps their impact can be better elaborated prior.

Response: Thank you for your useful suggestion. Although a systematic and comprehensive search was performed, the included studies are only from China. Therefore, our hope is that the topic will receive more attention from surgeons in other countries. If high-quality research is published in the future, the meta-analysis will be update. In addition, the potential global impact of the research has been described in the discussion.

Reviewer 3:

Comments 1: Reflux gastritis and residual gastritis Comment: The difference between reflux gastritis and residual gastritis is still unclear. In the Definitions section, the authors described the definition of reflux gastritis, but not a definition of residual gastritis. Reflux gastritis means residual gastritis due to bile reflux, as the authors stated. Residual gastritis may include atrophic or metaplastic gastritis due to H.pylori infection, but I think that reflux gastritis and residual gastritis are basically the same. Therefore, I would like to suggest the following three options this time: 1. Simply remove the results of residual gastritis. 2. Combine the results of reflux gastritis and residual gastritis. 3. Describe the definition of residual gastritis in detail, especially the difference from reflux gastritis. Please choose one of the three suggestions and consider revising the manuscript.

Response: Thank you for your kind suggestion. We have removed the results of residual gastritis to make the section easier to understand.

Comments 2: Figure 1 Study flow diagram Comment: The total number of reports searched in Pubmed, Web of Science, Cochrane Library, Embase and CNKI was 771. However, the number of identified reports is described as 908. Please correct any errors in the numbers or add the description of "Others (n=137)". Furthermore, screened

records was 693, and excluded records was 657. Therefore, reports sought for retrieval must be 36. However, the authors' description was 35. This is incorrect, please correct.

Response: Thank you for your useful suggestion. We have checked the data in the diagram and corrected it.